Kidney and hypertension

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Kidney and hypertension. There is a unique relationship between the kidney and blood pressure (BP): on the one hand, renal dysfunction and particularly renal disease cause an increase in BP, while on the other hand, high BP accelerates loss of function of the diseased kidney. Transplantation studies, both in experimental animals and humans, documented that “blood pressure goes with the kidney,” a normotensive recipient of a kidney genetically programmed for hypertension (HT) will develop HT, while conversely hypertensive patients with renal failure receiving the kidney of a normotensive donor may develop normotension. Family studies showed higher BP values and more frequent HT in first degree relatives of patients with primary glomerulonephritis or diabetic nephropathy, both type 1 and type 2. The notion that HT accelerates the loss of renal function has been proposed at the turn of the century, but definite evidence by observational and interventional studies has only been provided in the last two decades. The issue has been much confounded by the mistaken belief that damaged kidneys require higher BP values in order to function properly. The mechanisms of BP increase in renal disease comprise: salt retention, inappropriate activity of the renin-angiotensin system (RAS) and of the sympathetic nerve system as well as impaired endothelial cell-mediated vasodilatation. There is ample evidence both in primary renal disease (AIPRI and REIN trials) and in nephropathy of type 1 and type 2 diabetes (IDNT, RENAAL) that pharmacological blockade of the RAS by angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers has BP-independent renoprotective effects. More recently, it has also been shown that blockade of the sympathetic nerve system has BP-independent effects on albuminuria and on glomerulosclerosis.

ROLE OF THE KIDNEY IN THE GENESIS OF HYPERTENSION

Guyton [1] proposed the hypothesis, supported by experimental evidence, that the disturbance of the blood pressure (BP)/natriuresis relationship (“renal function curve”) is responsible for the BP elevation when renal function is impaired. Because the gain of the BP-natriuresis relationship overrides all other regulatory systems, the ultimate determinant of BP must be renal handling of sodium according to this concept. This does not imply that hypertension (HT) is a renal disease, but indicates that a renal functional abnormality, i.e. disturbed BP/natriuresis relationship, is a sine-qua-non condition for the development of any type of HT.

Early studies of Bianchi et al [2] and more definite well controlled experimental studies of Rettig et al [3, 4] showed that “blood pressure goes with the kidney.” Transplantation of the kidney from a genetically hypertension-prone donor rat, even when it had been kept normotensive from weaning by antihypertensive medication, caused progressive increase of BP in a recipient animal which was immunologically manipulated to prevent a rejection reaction. In contrast, and quantitatively less impressive, transplantation of a kidney graft from a donor genetically programmed for normotension provoked normotension in the recipient.

There is also some analogous evidence in humans. Recipients of grafts of genetically hypertension-prone donors required more antihypertensive medication [5] and recipients of kidneys from donors dying from cerebral hemorrhage, presumably because of hypertension, had a higher risk to develop hypertension [6]. Conversely, patients who had become dialysis-dependent because of hypertension-induced renal injury turned normotensive after the kidney of a normotensive donor had been successfully grafted [7].

RELATION BETWEEN RENAL DISEASE AND BLOOD PRESSURE

A classical concept had been that renal disease causes hypertension. Individuals with renal disease develop hypertension, as had indirectly been concluded very elegantly by Richard Bright [8]. As early as 1923 Franz Volhard postulated: “I doubt very much whether hypertension has any useful purpose. We are confronted with a vicious circle which is responsible for progression of hypertensive renal disease and the final outcome of renal insufficiency” [9].

It has recently emerged that the relation is more com-
Table 1. Blood pressure status of parents with biopsy-confirmed glomerulonephritis and controls (after [10])

<table>
<thead>
<tr>
<th></th>
<th>Glomerulonephritis (N = 39)</th>
<th>Control (N = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>36 (57%)</td>
<td>45 (33%)</td>
</tr>
<tr>
<td>Borderline hypertensive</td>
<td>7 (11%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Normotensive</td>
<td>20 (32%)</td>
<td>82 (59%)</td>
</tr>
</tbody>
</table>

Significant difference (by $\chi^2$ test) between hypertensives versus others with glomerulonephritis and controls. Definitions are: hypertensive, blood pressure $\geq 160/95$ mm Hg or on antihypertensive medication; borderline hypertensive, blood pressure 140–159/90–94 mm Hg; normotensive, blood pressure $<140/90$ mm Hg.

Table 2. Blood pressure and urinary albumin excretion in offspring of parents with type 2 diabetes according to absence or presence of diabetic nephropathy in the parents (after [12])

<table>
<thead>
<tr>
<th>Parents type 2 diabetes</th>
<th>Offspring (N = 30)</th>
<th>Offspring (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without nephropathy</td>
<td>With nephropathy</td>
</tr>
<tr>
<td>Ambulatory blood pressure</td>
<td>117 ± 12.9</td>
<td>125 ± 16.9</td>
</tr>
<tr>
<td>Albumin excretion rate</td>
<td>4.8 (0.36–17.5)</td>
<td>7.8 (1.04–19.0)</td>
</tr>
<tr>
<td>Increase in urinary albumin</td>
<td>6.3-fold (1.5–231)</td>
<td>16-fold (1.2–236)</td>
</tr>
</tbody>
</table>

complex. While undoubtedly renal disease causes hypertension, there is increasing evidence that a genetic predisposition to hypertension increases the risk to develop renal disease. This has been shown in patients with glomerulonephritis (Table 1) [10]. Blood pressure values were higher in the parents of patients with glomerulonephritis than in the parents of matched controls. The same is true for diabetic nephropathy. Higher blood pressure values were found in parents of type 1 diabetic patients as compared to parents of patients without diabetic nephropathy [11]. In offspring of type 2 diabetic patients with as compared to offspring of type 2 diabetic parents without diabetic nephropathy, Strojek et al [12] found higher blood pressure values by ambulatory blood pressure measurement (Table 2). In the offspring of diabetic parents with nephropathy, blood pressure was also sodium-dependent compared with offspring of diabetic parents without hypertension.

Another misconception had been that in order for BP to rise, an impairment of glomerular filtration rate (GFR) was necessary. This is definitely not the case. In children with a nephrotic syndrome, Küster et al [13] found that blood pressure values, although remaining within the range of normotension, were systematically higher during the nephrotic episode than after remission of the disease. That a reduction of total kidney GFR is not a pre-condition for the increase in BP was also shown by Stefanski et al (Table 3) [14]. In patients with biopsy-confirmed IgA glomerulonephritis and normal inulin clearance, he observed higher 24 h BP values, and this was accompanied by greater septal thickness and evidence of impaired compliance of the left ventricle.

In the distant past it was well known that hypertension may cause renal failure in the absence of primary renal disease. The most frequent cause for this was malignant hypertension, i.e. a phase of accelerated hypertension with arteriolar necrosis [15, 16]. There is also evidence, however, that even in the absence of malignant hypertension, renal failure may develop, although this presumably is a slow process requiring decades to develop. Perera [17] noted that during long-term follow-up, renal failure developed in 92 of 500 patients with essential hypertension. More recently, Klag et al [18] and Perry et al [19] showed a relation between baseline BP and ESRD in patients without a priori evidence of renal disease. The evidence that such progressive slow renal damage is preventable with antihypertensive agents is not perfectly convincing [20]. It may be argued, however, that in these studies target blood pressure had not been sufficiently low [21].

**RELATIONSHIP OF BLOOD PRESSURE AND PROGRESSION OF RENAL FAILURE**

Despite the above postulate of Volhard [8] it took decades until the deleterious effect of high BP values on progression could be proven first by observational studies in diabetic [22, 23] and later non-diabetic renal disease [24]. In patients with non-diabetic renal disease even more time was required before definite evidence was provided by interventional trials that lowering of blood pressure effectively attenuated the rate of progression in patients with proteinuria exceeding 1 g/day [25].

**WHAT IS THE APPROPRIATE TARGET BLOOD PRESSURE?**

There is good evidence that there is a continuous increase of renal risk with increasing blood pressure without a definite threshold. One piece of observation comes from the study of Opelz et al [26] that in renal graft recipients (as one model of renal damage) 6 year graft survival is progressively worse with increasing levels of systolic blood pressure (Fig. 1). This concept has recently been confirmed by a meta-analysis of controlled intervention trials in patients with non-diabetic renal disease where the best renal prognosis was found in individuals with systolic BP $<110$ mm Hg (abstract: Jafar TH J Am Soc Nephrol 11:63A, 2000).

It is likely, but currently not definitely proven that
Table 3. Blood pressure status in patients with IgA glomerulonephritis and normal inulin clearance (after [14])

<table>
<thead>
<tr>
<th></th>
<th>Casual BP mm Hg</th>
<th>24-hour BP</th>
<th>Day-time BP</th>
<th>Night-time BP</th>
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<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>125</td>
<td>80</td>
<td>124.5</td>
<td>76.5</td>
</tr>
<tr>
<td>Matched controls</td>
<td>120</td>
<td>72.5</td>
<td>114.5</td>
<td>70.5</td>
</tr>
<tr>
<td>P</td>
<td>0.04</td>
<td>0.04</td>
<td>0.007</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Fig. 1. Association of systolic blood pressure at 1 year after transplantation with subsequent graft survival in recipients of cadaver kidney transplants. Data taken from Opelz et al [26], reprinted with permission.

Fig. 2. Rate of glomerular filtration rate (GFR) decline, dependent on blood pressure and proteinuria. Symbols are: (dashed line) proteinuria <1 g/day; (solid line) ≥1 g/day. Data are taken from Peterson et al [25], reprinted with permission.

Fig. 3. Relationship between irbesartan dose and peak renal blood flow (RBF) response in healthy subjects and patients with type 2 diabetes mellitus. Despite the fact that type 2 diabetic patients with nephropathy is a low-renin state and that the plasma renin activity (PRA) was lower, the renal vascular response to irbesartan was significantly higher in diabetic patients (P < 0.01). Symbols are: (●) diabetics; (□) normals. Data are taken from Price et al [38], reprinted with permission.

Ambulatory blood pressure (ABPM) is more predictive than office BP, particularly an attenuation of the night-time decrease of BP [27]. In patients with IgA glomerulonephritis [28], as well as in patients with more advanced diabetic [29] and non-diabetic renal disease [30], patients with attenuated night-time decrease of BP (non-dippers) had a greater rate of loss of endogenous creatinine clearance than dippers. In type 2 diabetic patients, Nakano et al found that patients with an obliterated night-time decrease of BP had a 20-fold higher rate of death (unad-
Table 4. Selected studies showing renoprotection properties of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor type 1 antagonists (AT-1-RB)

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>583</td>
<td>323</td>
<td>409</td>
<td>1715</td>
<td>1513</td>
</tr>
<tr>
<td>Planned duration of follow-up years</td>
<td>3.0</td>
<td>2.2</td>
<td>3.0</td>
<td>2.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Study medication (ACEI or AT-1-RB)</td>
<td>Benazepril</td>
<td>Ramipril</td>
<td>Captopril</td>
<td>Irbesartan</td>
<td>Losartan</td>
</tr>
<tr>
<td>Dosage of study medication mg/day</td>
<td>10</td>
<td>1.25-5.0</td>
<td>75</td>
<td>75-300</td>
<td>50-100</td>
</tr>
<tr>
<td>Baseline serum creatinine concentration μmol/L</td>
<td>186</td>
<td>194</td>
<td>115</td>
<td>148</td>
<td>168</td>
</tr>
<tr>
<td>Relative risk (95% CI) of ESRD in the treated group</td>
<td>0.89</td>
<td>(0.06-14.2)</td>
<td>(0.30-0.87)</td>
<td>0.50</td>
<td>0.83</td>
</tr>
<tr>
<td>Relative risk (95% CI) of doubling serum creatinine in the treated group</td>
<td>0.44</td>
<td>0.47</td>
<td>0.48</td>
<td>0.71</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*Mainly non-diabetic nephropathy; diabetic nephropathy was a cause of renal insufficiency only in 21 of 583 patients

*Combined end points (death, dialysis or kidney transplantation) relative risk

Does Selection of Antihypertensive Agents Matter?

There is overwhelming evidence for a role of angiotensin II in progression, both by hemodynamic and by non-hemodynamic factors [36]. It is of interest, however, that pharmacological blockade of the renin-angiotensin system (RAS) is renoprotective even in states where presumably the RAS is suppressed, as indicated by circulating plasma renin activity. This paradox can be explained by recent observations that within the kidney, the RAS is activated not only in the juxtaglomerular apparatus, but also in tubular epithelial cells [37]. This has been shown in the ablation model, but is also true in diabetes and in ageing. Price et al [38] showed that the increment in renal plasma flow upon administration of an angiotensin receptor blocker, i.e., an index of the angiotensin II-dependency of renal vascular tone, was higher in type 2 diabetic patients despite low plasma renin activity (Fig. 3). It has recently been shown that such suprasensitivity to angiotensin II type 1-receptor blockade was present only under conditions of the hyperglycemic clamp, not under conditions of euglycemia [39]. In line with this observation, Wagner et al [40] found that the expression of angiotensin II type 1-receptor mRNA in biopsies of patients with glomerulonephritis or diabetic nephropathy was low, consistent with the notion of homeostatic down regulation of the receptor in response to high intrarenal angiotensin II concentrations.

Today there is no more doubt that pharmacological blockade of the RAS by administration of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor type 1 blockers (AT-1-RB) provides blood pressure-independent renoprotection. The major studies, i.e., AIPRI [41] and REIN [42], Lewis et al trial in type 1 [43] and IDNT [44] and RENAAL [45], respectively, in type 2 diabetes are summarized in Table 4.

Today there is widespread consensus that in patients with proteinuric renal disease, blood pressure should be lowered to values below the currently accepted upper value of normotension, i.e., 130/85 mm Hg [33, 34]. Most authorities propose a target blood pressure of 120/75 mm Hg [34, 35].
pressure. Non-hypotensive doses of the central sympathicomplegic agent moxonidine reduced the development of glomerulosclerosis and of albuminuria in subtotal nephrectomized rats [55]. That this effect is not unique to the centrally acting drug moxonidine is shown by further experiments: metoprolol at doses which failed to affect systemic blood pressure [56], or surgical denervation of the kidney (abstract; Odoni G, J Am Soc Nephrol 11:626A, 2000) had a similar renoprotective effect. The in vivo relevance of these observations in humans is documented by the observation of Strojek et al, who showed that moxonidine at doses that did not affect blood pressure caused significant lowering of albumin excretion in the morning urine in normotensive, non-smoking microalbuminuric type I diabetic patients [57].

It emerges from the above that many details concerning blood pressure in the kidney are currently unresolved. It is also certain, however, that antihypertensive treatment has become the most effective therapeutic intervention available today to retard progressive loss of renal function.

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REFERENCES


